Kidney Function in Obesity—Challenges in Indexing and Estimation

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As the prevalence of obesity continues to increase worldwide, an increasing number of people are at risk for kidney disease. Thus, there is a critical need to understand how best to assess kidney function in this population, and several challenges exist. The convention of indexing glomerular filtration rate (GFR) to body surface area (BSA) attempts to normalize exposure to metabolic wastes across populations of differing body size. In obese individuals, this convention results in a significantly lower indexed GFR than unindexed GFR, which has practical implications for drug dosing. Recent data suggest that "unindexing" estimated GFR (multiplying by BSA/1.73 m^2) for drug dosing may be acceptable, but pharmocokinetic data to support this practice are lacking. Beyond indexing, biomarkers commonly used for estimating GFR may induce bias. Creatinine is influenced by muscle mass, whereas cystatin C correlates with fat mass, both independent of kidney function. Further research is needed to evaluate the performance of estimating equations and other filtration markers in obesity, and determine whether unindexed GFR might better predict optimal drug dosing and clinical outcomes in patients whose BSA is very different than the conventional normalized value of 1.73 m^2.

Keywords: Obesity, Glomerular filtration rate, Indexing, Scaling, eGFR

INTRODUCTION

The prevalence of obesity (body mass index [BMI] ≥30 kg/m^2) continues to increase in both developed and developing countries.[1] Recent estimates from the National Health and Nutrition Examination Survey (2013-2014) report prevalence of obesity of 37.7%, and class III obesity (BMI ≥40 kg/m^2) of 7.7%, up from 33.9% and 5.7% in 2007 to 2008.[2,3] Among the US population with CKD, the prevalence of obesity and class III obesity is even higher, at 44.1% and 22.2%, respectively.[4] Both kidney disease and obesity have important implications in terms of prognosis and drug dosing; however, methods for estimating kidney function in the setting of obesity—particularly severe obesity—remain uncertain. In this review, we examine the rationale for indexing glomerular filtration rate (GFR) to body surface area (BSA), methods to estimate GFR, and the accuracy and clinical implications of these conventions in the obese population. Finally, we highlight areas requiring additional research in the growing population of obese individuals.

RATIONALE FOR INDEXING GFR TO BSA

To fully understand the issues inherent to the assessment of kidney function in obesity, we must first discuss the rationale underlying the convention of indexing GFR to BSA. Across mammalian species, GFR increases as kidney and body mass increases. This relationship follows the power law equation ($y = aX^b$), where y is the GFR, a is a constant, X is the body mass, and the coefficient b is estimated to be 0.77 to 0.79.[5,6] This "$^3/_4$ power" relationship between GFR and body mass is similar to the relationship between metabolic rate and body mass, suggesting that GFR increases proportionally to metabolic needs, which makes physiological sense. In a similar manner, higher glomerular number (power law coefficient 0.57-0.62) and, to a lesser extent, glomerular capillary tuft volume (power law coefficient 0.26-0.29) are associated with higher body mass.[5]

BSA provides a critical role in dissipating heat produced through metabolic processes, although recent literature suggests that scaling of metabolism is complicated and that substantial variation exists in animals.[6,7] Because BSA is a 2-dimensional variable whereas volume (body mass) is a 3-dimensional variable, smaller animals have a higher BSA to body mass ratio than larger animals. For example, a mouse has a relatively higher metabolic rate and GFR per body mass (0.2 mL/min, or about 0.007 mL/min/g body weight) than a horse (390 mL/min, or about 0.0008 mL/min/g body weight).[6] Allometric scaling was first used to standardize GFR in humans in studies published in the early 20th century, based on the observation that correction for BSA tended to normalize rates of urea excretion.[8,9]

However, there is controversy over the most appropriate scaling variable, as physiological rationale exists for other factors such as resting energy expenditure (REE) or total body water (TBW) because the kidneys help excrete metabolic wastes and regulate fluid and electrolyte balance. Ellam and colleagues[10] used data from the Chronic Renal Insufficiency Cohort (CRIC) study and the Modification of Diet in Renal Disease (MDRD) study to examine gender differences in metabolic burden. Men had higher 24-hour urine urea excretion and serum urea nitrogen levels than women; indexing to BSA only slightly attenuated these gender differences. When GFR was indexed to estimated REE, differences between 24-hour urine urea nitrogen and serum urea nitrogen levels were mostly abolished.

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When GFR was indexed to estimated TBW, serum urea nitrogen levels were similar between genders, but the relationship was reversed for 24-hour urea nitrogen (higher in women than men). Thus, indexing to BSA results in a greater metabolic burden in men compared with women, whereas indexing to REE or TBW may help reduce these differences.

Daugirdas and colleagues[11] used data from 1551 potential kidney donors evaluated between 1973 and 2005 to examine different methods of indexing GFR measured with ^{125}I-iothalamate. Mean BMI was 27.2 kg/m^2 for men and 26.3 kg/m^2 for women. Scaling parameters included equation-based estimates of BSA, TBW, metabolic rate, and liver size. Mean unindexed GFR was 122 mL/min in men and 106 mL/min in women. Indexing to TBW resulted in women having higher indexed GFR (119 mL/min) than men (105 mL/min), whereas indexing to BSA, or liver size, resulted in similar mean indexed GFR for men and women (113 mL/min/1.73 m^2 for men and women using both methods). Furthermore, indexing to BSA resulted in the most uniform indexed GFR across quintiles of BSA (Q1-5: 107, 103, 106, 103, and 104 mL/min/1.73 m^2, respectively). Thus, if GFR adjusted for a body size scaling variable should be similar across a population, then BSA seems to be appropriate.

CLINICAL SUMMARY

- Indexing glomerular filtration rate (GFR) to body surface area results in lower indexed GFR than unindexed GFR in obese individuals, which has implications for drug dosing and risk stratification.
- Creatinine levels are directly related to muscle mass, and cystatin C appears to correlate with fat mass, independent of kidney function.
- Studies examining the performance of estimating equations in obesity have shown varied results; some have found that creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation overestimates indexed GFR in severely obese patients.
- While limited data suggests that "unindexing" eGFR provides reasonable estimates of unindexed GFR, more research is needed to determine whether unindexed GFR may better optimize drug dosing or prognosticate risk than indexed GFR, particularly in individuals at extremes of body size.

EVIDENCE FOR INDEXING TO BSA FROM THE DIALYSIS POPULATION

Another interesting way to compare different methods of indexing GFR is to examine patient outcomes by hemodialysis adequacy, which is commonly assessed as Kt/V (where K is the urea clearance of dialyzer, t is the dialysis time, and V is the volume of distribution of urea, which approximates TBW). Several studies have identified limitations of using V as an indexing variable for a given BSA, V is lower in smaller individuals than larger individuals.[6,12] This may have resulted in hemodialysis treatment disparities for smaller individuals. For instance, V is on average lower in women than men, and women are often prescribed treatments of shorter duration.

Port and colleagues[13] examined the association between dialysis dose and body size with mortality in 45,967 incident hemodialysis patients. Dialysis dose was divided into 5 groups—urea reduction ratio (URR) <60, 60 to 65, 65 to 70, 70 to 75, and >75, corresponding to single pool Kt/V KT/V cutpoints of <1.1, 1.2, 1.32, 1.5, and >1.7. Lower BMI and lower dialysis dose were both associated with increased risk of death. When stratified by tertiles of body size (BMI—small <23.1 kg/m^2, medium, 23.2-27.8 kg/m^2, large, >27.8 kg/m^2), higher dialysis dose was associated with lower mortality in all 3 categories. However, small and medium BMI groups had significantly lower mortality at the highest dose compared with the next highest dose (URR >75 compared with URR 70-75), whereas the large BMI group had similar mortality at URR >75 and URR 70-75.

In the Hemodialysis study, a multicenter randomized controlled trial of dialysis dose and membrane flux, women randomized to the higher dialysis dose of single pool Kt/V (spKT/V) of 1.65 had significantly lower mortality than women randomized to the conventional lower dose of spKT/V 1.25 (RR 0.81, $P = .02$), whereas there was no significant effect of the higher dialysis dose on men (relative risk [RR] 1.16, $P = .2$) compared with the standard dose.[12] The same investigators examined whether rescaling dialysis dose to BSA helped explain the different responses in women vs men.[14] Dose of dialysis, when BSA-adjusted, was on average 12.3% lower in women compared with men in the conventional dialysis dose group. The ratio V/BSA modified the effect of dialysis dose on mortality; higher dialysis dose was associated with decreased mortality among those with lower V/BSA and marginally associated with increased mortality among those with higher V/BSA. These studies would suggest that for scaling metabolic wastes in patients on dialysis, TBW may not be an optimal scaling variable; consideration of other scaling variables such as BSA may be helpful.

PROBLEMS WITH INDEXING GFR TO BSA IN THE SETTING OF OBESITY

When the process of indexing GFR to BSA first came into favor, average American BSA at age 25 years was 1.73 m^2.[8] This value is still used in indexing today even as weight and BSA distributions have shifted higher (National Health and Nutrition Examination Survey 2011-2014: women 1.81 m^2, men 2.05 m^2).[15] In obese patients, indexed GFR is substantially lower than unindexed GFR and thus could have implications in CKD staging and drug dosing.[16] For instance, a hypothetical 5′10″ man with unindexed GFR of 90 mL/min would have a similar indexed GFR of 87 if he had a BMI of 20 kg/m^2, using the DuBois equation (Table 1). However, if he had a BMI of 40 or 60 kg/m^2, indexed GFR would be 65 or 54 mL/min/1.73 m^2, respectively. Another issue is the validity of BSA-estimating equations, which were not derived in obese populations. Hypothetical results for the example using formulas by Mostellar[17] and Haycock and colleagues[18] are also shown in Table 1.